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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/300,959	04/27/99	ZANETTI M	P-ZA-3519

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EXAMINER	
STROUP, C	
ART UNIT	**PAPER NUMBER**
1633	10

DATE MAILED: 10/25/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

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U.S. G.P.O. 2000 - 465-189/25268

Office Action Summary

Application No.	Applicant(s)
09/300,959	Zanetti
Examiner	**Group Art Unit**
Stroup, Carrie	1633

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *3, 4, 18-21, and 29-32* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *3, 4, 18-21, and 29-32* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 4

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Applicant's request for priority to the provisional application 60/0833,154 is denied for claims 3, 4, 20 and 21.

Said provisional comprises a cover sheet and a copy of Gerloni et al (*DNA and Cell Biology*, 5 November 1997, 16: 611-625). The pending claims 3 and 4 are drawn to a method of stimulating an immune response, while claims 29-32 are directed to methods of treatment, wherein said claims utilize a nucleic acid molecule encoding a heterologous epitope under the operational control of a hematopoietic expression element. It is noted that the provisional application discloses only one such vector, γ1NANP, comprising a heterologous epitope (NANP) under the operational control of a hematopoietic expression element, which was not demonstrated to elicit an immune response in vivo, but instead was used to assay for mRNA transcription (pg 617, Figure 3; pg 612, col. 2, para. 1). Additionally, the provisional was void of any teachings pertaining to use of said vector for methods of treatment in vivo. Therefore, the provisional application does not provide an enabling disclosure for the claims 3, 4, and 29-32. Additionally, claims 20 and 21 encompass a fusion protein with a cytokine, and under the operational control of hematopoietic cell expression elements, yet the provisional application fails to disclose any vector comprising a cytokine. Said provisional only provides an enabling disclosure for the intrasplenic administration of a vector encoding a murine rearranged V_H region joined with a genomic human γ1 C region and under the operational control of a lymphoid tissue-specific promoter and enhancer (pg 615, col. 2, para. 1; pg 622, col. 1, para. 2). Therefore, the pending claims 3, 4, 20, 21, and 29-32 are clearly not supported by the claimed provisional application.

Applicant's election with traverse of Group II in Paper No. 8, filed 7/26/00, is acknowledged. The traversal is on the ground(s) that Groups II and III are improperly separated because a thorough search of the claims of either group would reveal art relevant to the examination of the other group. This is not found persuasive because Group II comprises vectors encoding any heterologous epitope fused which may comprise a cytokine sequence, while the

invention of Group III is limited to vectors encoding an immunoglobulin molecule. The groups are patentably distinct because the two vector compositions encode proteins which have widely variant in structure and function, e.g., cytokines with any type of epitopes versus immunoglobulins, which have acquired a separate classification in the art. Although, a search of one might reveal art in the other group, said search is not a sufficient and thorough search of the art in the other group. Additional efforts on the part of the Examiner would still be required to search both groups completely. The requirement is still deemed proper and is therefore made FINAL. Claims 1, 2, 5-17, 22-28, and 33 withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected group, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 8.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 3, 4, 18-21, and 29-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of stimulating an immune response against *Plasmodium falciparum malaria sporozoites* by administering the γ1NANP, γ1NANP/GM-CSF, or γ1NANP/IL-2 vector intrasplenically and a method of treating *Plasmodium falciparum malaria sporozoites* in mice with γ1NANP/GM-CSF administered intrasplenically, does not reasonably provide enablement for a method of stimulating an immune response, or a method of treating a condition, by administering to a lymphoid tissue a nucleic acid molecule comprising a hematopoietic expression

element linked to nucleic acid molecule encoding one or more heterologous epitopes which may also be fused to a cytokine. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant's claimed invention is to a method of treating a condition and stimulating an immune response comprising administering a nucleic acid molecule comprising a hematopoietic cell expression element operationally linked to a nucleic acid sequence encoding a heterologous polypeptide, wherein said nucleic acid molecule is targeted to a hematopoietic cell *in vivo* or *ex vivo*. The specification provides exemplifications in which plasmid vectors encoding fusion proteins comprising human γ1 C region gene, wherein the murine GM-CSF or IL-2 coding sequence was cloned at the 3' end of the CH3 domain, was fused with the murine V_H^{62} gene, wherein the CDR3 region has been modified to encode three repeats of Asn-Ala-Asn-Pro (NANP) sequence of the *Plasmodium falciparum malaria sporozoites* (Figure 19, and pg 14, lines 23-pg 17, line 19). Said constructs were injected intrasplenically into rel B (-/-) C57Bl/6 mice which carry a mutation in the relB subunit of the MF-κB complex thus lacking bone marrow-derived mature dendritic cells. Said mice which were injected with vectors comprising GM-CSF displayed a marked increase in IgG1 antibody production in comparision to equivalent vectors which did not contain a cytokine (γ_1NANP) or with the IL-2 vectors (γ_1NANP/IL-2), wherein the applicant states that "These results demonstrate that administration of a nucleic acid molecule encoding an epitope fused to GM-CSF promotes the IgM to IgG switch." (Pg 105, lines 21-24). Additionally, further experiments with γ_1NANP/GM-CSF utilized for priming and boosting in said mice demonstrated that GM-CSF heightens the anamnestic response induced by injection of *P. falciparum sporozoites* wherein the specification discloses that "booster by parasites is equivalent to a challenge response or restimulation by infection" (pg 109, lines 9-12).

The specification fails to provide an enabling disclosure for a method of stimulating an immune response or a method of treatment of any and all conditions other than *P. falciparum sporozoites* infection in mice via intrasplenic

injection of γ_1NANP/GM-CSF. The specification does not disclose other medical conditions which would respond to treatment from the disclosed vectors and methods of use, to include the encoded antigens and dosing regimes. Additionally, the teachings within the specification for the use of the claimed invention in mice cannot be extrapolated to any and all species, to include humans, because of the unpredictability in the art of DNA vaccines and the failure of the specification to overcome this unpredictability by providing teachings specific to the use of the disclosed plasmids within other non-murine species. For example, McCluskie et al (*Molecular Medicine*, May 1999, 9: 267-300) teach that:

> "Route of administration of plasmid DNA vaccines influences the strength and nature of immune responses in mice and non-human primates. However, the results in mice were not always predictive of those in monkeys and this is likely true for humans as well. Optimal dose and immunization schedule will most likely vary between species. It is not clear whether results in non-human primates will be predictive of results in humans, thus addtional studies are required."

The specification also fails to provide an enabling disclosure for a method of treating *P. falciparum sporozoites* in the absence of priming and boosting with γ_1NANP/GM-CSF, such as γ_1NANP/IL-2 or γ_1NANP. The specification discloses that although γ_1NANP/IL-2 elicitied an immune response (e.g., Figure 20), said response was not demonstrated to prevent infection following challenge with *P. falciparum sporozoites* (Example VII, pg 105-107).

The specification also fails to provide an enabling disclosure for the use of hematopoietic expression elements other than those targeting expression to B cells. The specification does not disclose the nucleotide sequence of the expression elements in other hematopoietic cells, such as T cells. Transgene expression *in vivo* following cellular transfection in vivo or ex vivo is highly unpredictable especially when utilizing plasmid DNA, wherein the level and stability of gene expression is largely dependent upon the specific construct design to include regulatory sequences (Verma et al, Nature, 1997, 389: 239-242; pg 239, col. 3, para. 2). There are also barriers to the in vivo expression of DNA which the specification does not overcome due to its limited disclosure on methods of conducting gene therapy and vector targeting.

For example, Eck et al (Goodman & Gilman's The Pharmalogical Basis of Therapeutics, Chapter 8, 9th ed, 1995, pages 77-101) disclose that:

> "Processes that must be considered include the distribution of the DNA vector following in vivo administration; the fraction of vector taken up by the target cell population; the trafficking of the genetic material within cellular organelles; the rate of degradation of the DNA; the level of mRNA produced; the stability of the mRNA produced; the amount and stability of the protein produced; and the protein's compartmentalization within the cell, or its secretory fate, once produced." (Pg 82, para. 1)

The specification also fails to provide an enabling disclosure to the use of any route of administration or target tissue other than intrasplenic. The specification teaches the innoculation of mice intrasplenic, intramuscular, subcutaneous, and intravenous, utilizing plasmid DNA encoding a chimeric immunoglobulin H chain gene consisting of a murine rearranged V_H region under the operational control of B cell regulatory sequences (γ1WT), resulted in only the intrasplenic route providing a statistically significant antibody titer (pg 69, Table 1). The specification also fails to teach methods of delivery to other lymphoid tissues other than the splene, to include dosing regimes, and as previously stated above, the appropriate construct design to include regulatory sequences for targeted delivery of the vector to designated lymphoid tissues, such as urogenital tissue and Payer's patches. Applicants are reminded that vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example, Miller (1995, FASEB J., Vol. 9, pages 190-199) review the types of vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise

but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma (Sept. 1997, Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Crystal (1995, Science, Vol. 270, page 404-410) also reviews various vectors known in the art and indicates that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409). Therefore, in the absence of teachings for methods of targeted delivery to any lymphoid tissue using a hematopoietic expression element via any route of administration, one of skill in the art would be required to practice undue experimentation to utilize any vector other than γ1NANP, γ1NANP/GM-CSF, or γ1NANP/IL-2 intrasplenically to elicit an immune response to *P. falciparum sporozoites* and γ1NANP/GM-CSF intrasplenically to treat *P. falciparum sporozoites*.

3. Claims 3, 4, 18-21, and 29-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 3, 4, 18-21, and 29-32 are unclear as to the metes and bounds of "hematopoietic cell expression element". Does this denote a specific nucleotide sequence which is disclosed within the specification by a sequence identification number? Or does this refer to a class of expression elements, any of which could be used with the claimed invention to a elicit an immune response? Or does this refer to an expression element located within the major intron of an immunoglobulin heavy chain gene (see Gillies et al, Cell, 1983, 33: 717-728)..

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 3, 4, 18, and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Gerloni et al (*Nature Biotechnology*, 1997).

Applicant's claimed invention is to a method of stimulating an immune response to *Plasmodium falciparum* comprising administering to mice intrasplenically a nucleic acid molecule comprising a hematopoietic cell expression element, which may function in B cells, and which is operationally linked to a nucleic acid sequence encoding one or more heterologous epitopes.

Gerloni et al disclose that the intrasplenic inoculation of plasmid γ1NANP DNA in C57/B16 mice elicited a primary immune response against the CDR3 peptide NANP which reacted with *Plasmodium falciparum sporozoites* (Nature Biotechnology, pg 876, col. 2, para. 3). Therefore the claimed invention was clearly anticipated.

6. Claims 18 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Gerloni et al (*DNA and Cell Biology*, 1997).

Applicant's claimed invention is to a nucleic acid molecule encoding a heterologous polypeptide under the operational control of a hematopoietic expression element which functions in a B cell.

Gerloni et al disclose vectors encoding a murine rearranged V_H region joined with a genomic human γ1 C region and under the operational control of a lymphoid tissue-specific promoter and enhancer (pg 615, col. 2, para. 1; pg 622, col. 1, para. 2). Therefore, the claimed invention was clearly anticipated.

7. Claims 3, 4, 18-21, and 29-32 are rejected under 35 U.S.C. 102(b) as being anticipated by Gerloni et al (Eur J Immunol, Feb 1998, 28: 516-524).

Applicant's claimed invention is to a nucleic acid molecule and a method of stimulating an immune response and treating *Plasmodium falciparum* comprising administering to mice intrasplenically a nucleic acid molecule comprising a hematopoietic cell expression element, which may function in B cells, and which is operationally linked to a nucleic acid sequence encoding one or more heterologous epitopes or a polypeptide expressed as a fusion with a cytokine, such as GM-CSF.

Gerloni et al disclose γ1NANP/GM-CSF vector administered intrasplenically elicited an effective IgG1 response against *Plasmodium falciparum* (see entire articles). Therefore, the claimed invention was clearly anticipated.

8. Claims 3, 4, 18-21, and 29-32 are rejected under 35 U.S.C. 102(a) as being anticipated by Gerloni et al (Eur J Immunolo, Jun 1998, 28: 1832-1838).

Applicant's claimed invention is to a nucleic acid molecule and a method of stimulating an immune response and treating *Plasmodium falciparum* comprising administering to mice intrasplenically a nucleic acid molecule comprising a hematopoietic cell expression element, which may function in B cells, and which is operationally linked to a nucleic acid

sequence encoding one or more heterologous epitopes or a polypeptide expressed as a fusion with a cytokine, such as GM-CSF.

Gerloni et al disclose γ1NANP/GM-CSF vector administered intrasplenically elicited an effective IgG1 response against *Plasmodium falciparum* (see entire articles). Therefore, the claimed invention was clearly anticipated.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 3, 4, 18 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zanetti et al (US Patent 5,508,386 or 5,583,202) in view of Banerji et al (1983).

Applicant's claimed invention is to a nucleic acid molecule and a method of stimulating an immune response to *Plasmodium falciparum* comprising administering a nucleic acid molecule comprising a hematopoietic cell expression element, which may function in B cells, and which is operationally linked to a nucleic acid sequence encoding one or more heterologous epitopes.

Zanetti et al disclose vectors encoding NANP tetrapeptide of Plasmodium Falciparum within CDR3 region of the H chain which elicited anti-NANP antibodies in rabbits (5,508,386, col. 10, lines 49-66; 5,583,202, col. 12, Table 1). Zanetti et al does not disclose the use of hematopoietic cell expression elements.

Banerji et al disclose the use of lymphocyte specific cellular enhancer elements located within the joining region of the immunoglobulin heavy chain gene for use in a vector results in a two fold increase in the magnitude of correct β-globin gene transcripts (abstract).

In light of Zanetti and Banerji et al it would have been obvious to use hematopoietic expression elements in the construct of Zanetti comprising heterologous expression elements for the purpose of eliciting an immune response in vivo. One would have been motivated to use said expression elements because Banerji et al disclose a significant increase in functional proteins expressed under the operational control of said expression elements.

No claims are currently allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carrie Stroup whose telephone number is (703) 306-5439. The examiner can normally be reached on Monday through Friday from 8:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached at (703) 308-0447. The fax phone number for this Group is (703) 308-0294.

Carrie Stroup

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